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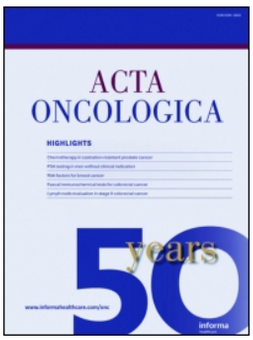

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Anti-androgen monotherapy versus gonadotropin-releasing hormone agonists in men with advanced, non-metastatic prostate cancer: a register-based, observational study

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ABSTRACT

Background: In randomised controlled trials, men with advanced, non-metastatic prostate cancer (PCa) treated with anti-androgen monotherapy (AA) had similar all-cause mortality as men treated with gonadotropin-releasing hormone (GnRH) agonists. Using real-world evidence (i.e., observational data), we aimed to further assess the difference in mortality between these two drug categories.

Material and Methods: We emulated a trial using data from Prostate Cancer data Base Sweden 3.0. We specifically focused on men diagnosed in 2006–2012 with high-risk PCa who had no distant metastasis. They either received primary hormonal therapy with AA ($n = 2078$) or GnRH agonists ($n = 4878$) who were followed for a median time of 5 years. Risk of death from PCa and other causes was assessed using competing risk analyses and Cox proportional hazards regression analyses, including propensity score matching.

Results: The cumulative 5-year PCa mortality was lower for men treated with AA (16% [95% confidence interval, CI, 15–18%]) than men treated with GnRH agonists (22% [95% CI 21–24%]). The 5-year other cause mortality was also lower for men on AA (17% [95% CI 15–19%] compared to men on GnRH agonists (27% [95% CI 25–28%]). In regression analyses, the risk of PCa death was similar, GnRH agonists versus AA (reference), hazard ratio (HR) 1.08 (95% CI 0.95–1.23), but the risk of death from all causes was higher for men on GnRH agonists, HR 1.23 (95% CI 1.13–1.34). Consistent results were seen in the propensity score-matched cohort.

Conclusion: Our results indicate that the use of AA as primary hormonal therapy in men with high-risk non-metastatic PCa does not increase PCa-specific mortality compared to GnRH. Using AA instead of GnRH agonists may result in shorter time on/exposure to GnRH-treatment, which may reduce the risk of adverse events associated with this treatment.

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Introduction

Radiotherapy with adjuvant hormonal therapy is the recommended treatment for men with high-risk prostate cancer (PCa) with no distant metastasis [1]. However, a substantial number of these men start primary hormonal therapy without radiotherapy, especially men with prostate specific-antigen (PSA) levels above 50 ng/mL and/or locally advanced PCa (clinical local stage T3-4) [2,3]. Moreover, around 20% of men diagnosed with localised PCa who received primary curative treatment will require hormonal therapy within 10 years [4].

The two main types of hormonal therapy for high-risk PCa with no distant metastasis are anti-androgen monotherapy (AA) and gonadotropin-releasing hormone (GnRH) agonists [5]. Their mechanism of action is very different. AAs competitively bind to androgen receptors, resulting in a decline in testosterone biosynthesis [6,7]. In contrast, GnRH agonists bind GnRH receptors on pituitary gonadotropin-producing cells, which causes a temporary release of LH and FSH. Thus, AA have less effect on a reduction of testosterone levels in the circulation as compared to GnRH agonists [8].

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Supplemental data for this article can be accessed here.

The adverse events profile for these two treatments is different, mainly due to these different effects on circulating testosterone levels. For men on AA, the most frequent adverse events are breast pain and gynaecomastia (due to conversion of testosterone into estradiol), while liver toxicity is a rare but serious event [9,10]. For men on GnRH agonists, the most common adverse events are hot flushes, weight gain, loss of libido and erectile dysfunction [8]. Additionally, GnRH agonists are associated with a number of long-term adverse metabolic effects including bone loss and increased risk of fractures [11], cardiovascular disease [12,13], diabetes mellitus type 2 [12] and possibly dementia [14]. Low levels of androgens have been shown to increase levels of low-density lipoprotein (LDL), triglycerides and insulin – all risk factors of ardiovascular disease [15]. Furthermore, testosterone may be protective against the development of atheromatous plaques by causing coronary artery dilation and inhibiting the effect of pro-inflammatory cytokines [16].

The current EAU-ESTRO-SIOG guidelines do not recommend AA with bicalutamide 150 mg/daily as standard of care for men with high-risk PCa with no distant metastasis [1]. This recommendation is based on a Cochrane review, which concluded that AA in men with advanced PCa is less effective than castration in terms of overall survival [17]. However, this review included studies with different types of AA and different dosages. Furthermore, in the subgroup analysis of men with advanced, non-metastatic PCa treated with bicalutamide 150 mg/daily, overall survival was similar to castration, in line with two randomised controlled trials (RCTs) [18,19]. These two RCTs specifically compared the clinical effectiveness as well as adverse events of bicalutamide 150 mg/daily versus GnRH agonists or maximal androgen blockade (GnRH agonist combined with continuous AA). Although the statistical requirement for non-inferiority was not met, survival was similar between the group of men treated GnRH agonists and those treated with bicalutamide 150 mg/daily. Based on these trials, the European Medicines Agency subsequently approved this AA for use in men with advanced, non-metastatic PCa [20].

Even though RCTs are considered the gold standard for evaluating the effectiveness of interventions, observational data, also known as real-world data, is an important addition to RCTs in clinical decision making provided that confounding by indication is appropriately handled [21]. Compared to patients outside RCTs, participants in RCTs are often highly selected with smaller cancer burden, and elderly patients and those with comorbidities are frequently excluded [22,23]. Thus, additional evidence from observational studies in support of results from RCTs is needed to show the external validity of these results.

When PCa cells escape the control of AA leading to disease progression, men on AA will switch to GnRH agonists [24]. Consequently, men who start on AA are less exposed to the broad/severe systemic and metabolic side effects of GnRH agonists than those who start on GnRH agonists. Hence, evaluating possible differences in PCa specific mortality and overall mortality amongst those starting on AA versus those starting on GnRH agonists is important.

We aimed to further investigate the potential difference in mortality between primary AA and GnRH agonists, by supplementing existing RCT evidence using real-world data.

Patients and methods

Data resource

The current study is based on data from Prostate Cancer data Base Sweden (PCBaSe) 3.0, which contains information on cancer characteristics and primary treatment from the National Prostate Cancer Register (NPCR) of Sweden [24]. Data on comorbidity were obtained from the Patient Registry, data on educational level, income and marital status from the LISA database, and cause and date of death from the National Cause of Death Registry.

Target trial

To ensure clinically meaningful results by use of real-world data, we used the ROBINS-I tool to emulate a target trial for risk of death in men on GnRH agonists or AA [25]. A target trial is a pragmatic trial that resembles a hypothetical RCT using observational data. Such an approach is considered useful when designing an observational study to assess the effects of different types of drugs. The ROBINS-I tool was used to assess potential biases before, during and after intervention in this study (See Supplemental Appendix) [25]. This tool was specifically designed to evaluate the risk of bias in comparative effectiveness studies that do not use randomisation to allocate individuals to comparison groups.

For this study, we selected all men from PCBaSe aged $\leq$90 years who were diagnosed with high-risk or regionally metastatic PCa, i.e., clinical local stage T3 or higher and/or PSA 20 ng/mL or higher and/or Gleason Grade Group 4–5 and/or N1 and no distant metastases. We specifically selected men diagnosed in 2006–2012 who received AA or GnRH agonists as primary therapy. The study then set out to compare AA monotherapy (150 mg/daily) with GnRH agonists. The large majority of men on AA received bicalutimide, for which adherence has previously been shown to be very good [26]. This information, as well as conversion from AA to GnRH agonists, was verified through data on filled prescriptions in the Prescribed Drug Registry. In case of disease progression, the switch to GnRH agonists was allowed and handled based on the intention-to-treat approach.

Follow-up was then calculated from the date of PCa diagnosis until death, emigration or date of censoring, whichever event came first. End of follow-up was 31 December 2015 for those analyses focused on PCa mortality, and 31 December 2016 for those analyses focused on all-cause mortality.

The Research Ethics Board at Umeå University Hospital approved the study.

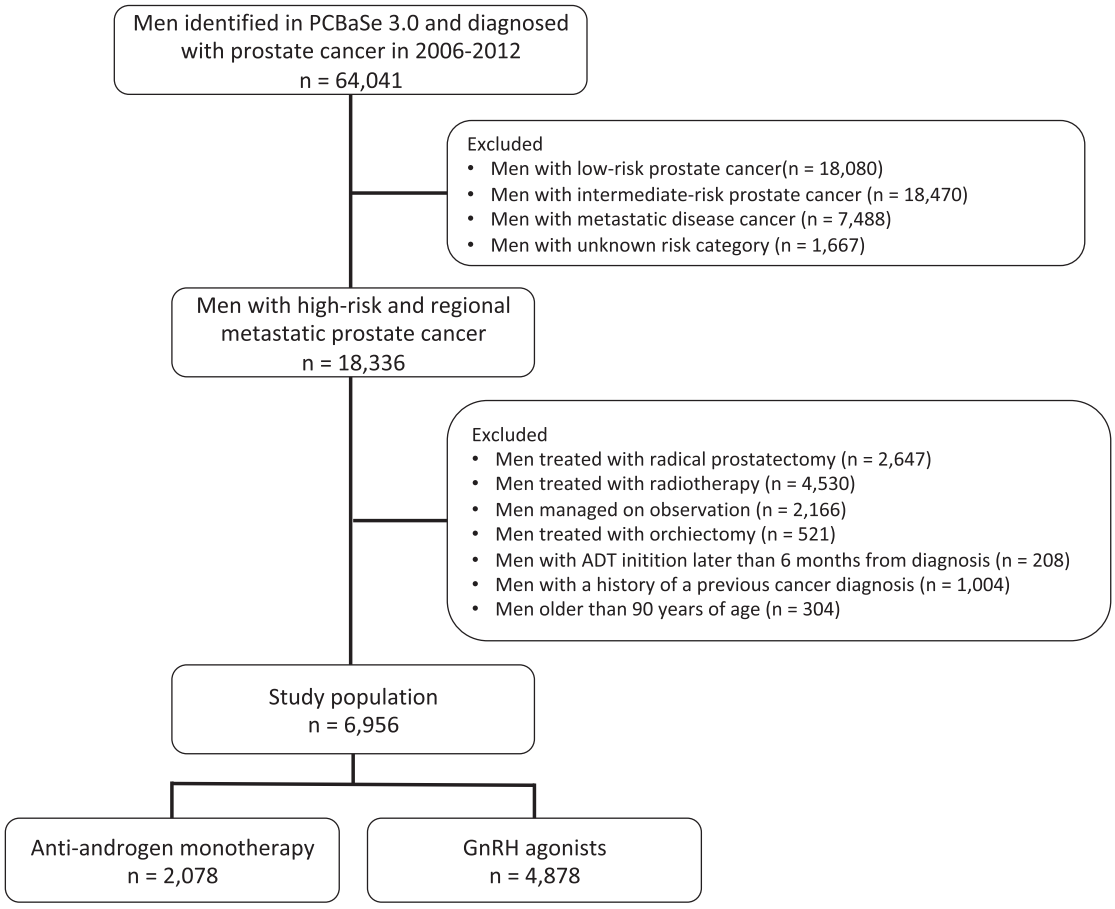

Figure 1. CONSORT diagram.

Imputation

To handle missing data for potential confounding factors, we performed multiple imputation using the method of Chained Equations and the MICE package [27]. Data were missing for the following variables: mode of detection (3% missing), T stage (1% missing), N stage (0.3% missing), Gleason Grade Groups (5% completely missing and 1% not differentiating between GGG1 or GGG2), percent positive biopsies (25% missing), PSA (1% missing) and education (1% missing).

Moreover, to account for differential misclassification of M1 disease, which included Mx when no bone scan was performed (prior to 2011), we conducted an inputation of M status (50% were recorded as Mx). In our imputation models, we included information from all men with intermediate-, high-risk, regionally metastatic and metastatic disease who were treated with primary hormonal therapy (Supplemental Table 1). The number of multiple imputations was set to five. All subsequent analyses were conducted using the imputed data sets, for men originally categorised with high-risk or regionally metastatic PCa, but excluding those with imputed M1 disease. A sensitivity analysis ignoring imputed M1 disease was also performed.

Statistical methods

First, we created cumulative incidence graphs showing PCa-specific death, overall death, and conversion from AA to GnRH agonists. Then, we conducted both traditional Cox proportional hazards regression analyses as well as propensity score-matched analyses within the target trial population. The latter allowed for a detailed assessment of our real-world data.

Cox proportional hazards regression analyses

We conducted uni- and multivariate Cox proportional hazards regression analyses for death of PCa and death from all causes using age as a timescale, whilst adjusting for year of diagnosis (continuous), mode of detection (categorical), T stage (categorical), Gleason Grade Groups (categorical), proportion positive biopsy cores (modelled as an interaction with T stage in men not diagnosed following TUR-P with two spine knots), PSA at diagnosis (categorical), bone imaging performed (dichotomised), Charlson comorbidity index (categorical), marital status (categorical) and education level (categorical). Results are presented as Hazard ratios (HR) with 95% confidence intervals (CI).

Propensity score matched analyses

We then conducted additional Cox model analysis based on propensity score matching for the type of hormonal therapy. Propensity score matching was done with the MatchIt package for R using a caliper of 0.1 and included the covariates enumerated above. Subsequent multivariable Cox proportional hazards regression analyses were performed adjusting for the

Table 1. Baseline characteristics of men in PCBaSe 3.0 diagnosed with high-risk and regionally metastatic prostate cancer in 2006–2012 and treated with anti-androgen monotherapy or GnRH agonists.

	Raw				Imputed*				Propensity score matched			
	Anti-androgens ($n = 2078$)		GnRH agonists ($n = 4878$)		Anti-androgens ($n = 2060$)		GnRH agonists ($n = 4740$)		Anti-androgens ($n = 1975$)		GnRH agonists ($n = 1975$)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Year of diagnosis												
2006–2007	542	26.1	1692	34.7	538	26.1	1638	34.6	527	26.7	547	27.7
2008–2010	559	26.9	1476	30.3	548	26.6	1415	29.9	532	26.9	532	26.9
2011–2012	977	47.0	1710	35.1	974	47.3	1687	35.6	916	46.4	896	45.4
Age at diagnosis, years												
<70	328	15.8	699	14.3	327	15.9	681	14.4	311	15.7	357	18.1
70–74	414	19.9	751	15.4	409	19.9	735	15.5	382	19.3	342	17.3
75–79	688	33.1	1287	26.4	682	33.1	1247	26.3	654	33.1	548	27.7
80–84	470	22.6	1367	28.0	464	22.5	1323	27.9	454	23.0	485	24.6
85–90	178	8.6	774	15.9	178	8.6	754	15.9	174	8.8	243	12.3
Mode of detection												
Screening	562	27.1	933	19.1	575	27.9	936	19.7	536	27.1	510	25.8
LUTS	1016	48.9	2836	58.2	1045	50.7	2852	60.2	1021	51.7	1058	53.6
Symptoms	431	20.8	966	19.8	440	21.4	952	20.1	418	21.2	407	20.6
Missing	67	3.2	139	2.9								
Clinical tumour category												
T1a	3	0.1	13	0.3	3	0.1	13	0.3	3	0.2	2	0.1
T1b	29	1.4	66	1.4	30	1.5	66	1.4	30	1.5	28	1.4
T1c	374	18.0	640	13.1	375	18.2	639	13.5	342	17.3	335	17.0
T2	639	30.8	1634	33.5	645	31.3	1612	34.0	629	31.8	652	33.0
T3	937	45.1	2207	45.2	932	45.2	2157	45.5	897	45.4	882	44.7
T4	76	3.7	262	5.4	75	3.6	253	5.3	74	3.7	76	3.8
TX	20	1.0	56	1.1								
N stage												
N0	150	7.2	262	5.4	150	7.3	263	5.5	145	7.3	133	6.7
N1	66	3.2	211	4.3	66	3.2	207	4.4	66	3.3	64	3.2
NX	1857	89.4	4392	90.0	1844	89.5	4270	90.1	1764	89.3	1778	90.0
Missing	5	0.2	13	0.3								
Gleason Grade Group												
GGG1	269	12.9	382	7.8	274	13.3	394	8.3	254	12.9	221	11.2
GGG2	412	19.8	652	13.4	444	21.6	725	15.3	415	21.0	385	19.5
GGG3	409	19.7	846	17.3	433	21.0	908	19.2	410	20.8	410	20.8
GGG4	547	26.3	1273	26.1	564	27.4	1308	27.6	552	27.9	568	28.8
GGG5	328	15.8	1377	28.2	345	16.7	1405	29.6	344	17.4	391	19.8
Missing	113	5.4	348	7.1								
Percent positive biopsy cores												
0–49%	452	21.8	623	12.8	570	27.7	838	17.7	528	26.7	507	25.7
50–74%	459	22.1	777	15.9	562	27.3	1049	22.1	526	26.6	499	25.3
75–100%	733	35.3	2121	43.5	928	45.0	2853	60.2	921	46.6	969	49.1
Missing	434	20.9	1357	27.8								
PSA at diagnosis, ng/ml												
<3	22	1.1	44	0.9	23	1.1	43	0.9	23	1.2	18	0.9
3–10	238	11.5	483	9.9	238	11.6	477	10.1	223	11.3	230	11.6
10–20	387	18.6	846	17.3	388	18.8	840	17.7	376	19.0	376	19.0
20–50	993	47.8	2151	44.1	988	48.0	2111	44.5	936	47.4	936	47.4
50+	423	20.4	1277	26.2	423	20.5	1269	26.8	417	21.1	415	21.0
Missing	15	0.7	77	1.6								
Charlson comorbidity index												
0	1217	58.6	2702	55.4	1206	58.5	2618	55.2	1148	58.1	1168	59.1
1	506	24.4	1153	23.6	501	24.3	1124	23.7	486	24.6	459	23.2
2	208	10.0	577	11.8	206	10.0	565	11.9	199	10.1	205	10.4
3+	147	7.1	446	9.1	147	7.1	433	9.1	142	7.2	143	7.2
Marital status												
Married	1388	66.8	3057	62.7	1375	66.7	2969	62.6	1315	66.6	1335	67.6
Not married	690	33.2	1821	37.3	685	33.3	1771	37.4	660	33.4	640	32.4
Education level												
High	392	18.9	679	13.9	394	19.1	670	14.1	367	18.6	335	17.0
Middle	716	34.5	1590	32.6	717	34.8	1564	33.0	682	34.5	689	34.9
Low	948	45.6	2532	51.9	949	46.1	2506	52.9	926	46.9	951	48.2
Missing	22	1.1	77	1.6								

*Results obtained after imputation of missing values and following matching on propensity score. Results from the first imputed dataset presented.

covariates used to perform the propensity score matching. Finally, we created 1-Kaplan-Meier estimates of PCa-specific and overall survival for the propensity score matched groups.

All statistical analysis was performed with R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

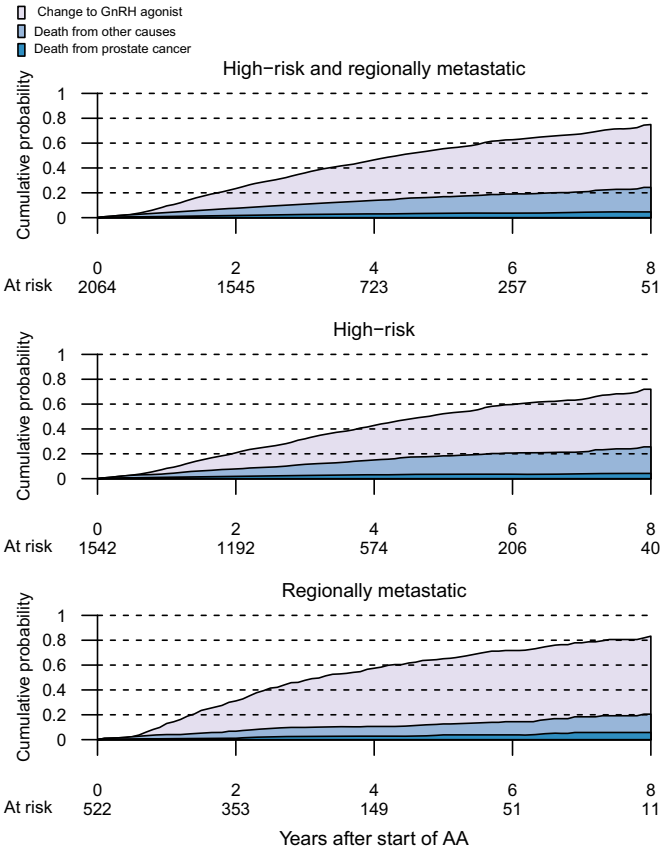

Figure 2. First event of conversion from AA to GnRH agonist, death from other causes or death from PCa assessed in competing risk analyses among men who started on anti-androgen monotherapy (AA) in competing risk analyses.

Results

The study population consisted of 2078 men on AA and 4878 men on GnRH agonists as primary hormonal therapy (Figure 1). The median follow-up was 4.7 years, representing a total of 28,315 person-years. Men treated with AA were younger, diagnosed in more recent calendar years, had less adverse cancer characteristics and had higher education level, compared to men treated with GnRH agonists (Table 1). Across the 5 imputed datasets, the number with imputed M1 disease ranged from 7 to 20 (mean =14) amongst those treated with AA and from 109 to 162 (mean =140) amongst those treated with GnRH agonists. In total, 765 (37%) men converted from AA to GnRH agonists, with a median time of exposure to AA of 4.3 years (95% CI 4.1–4.6) (Figure 2).

The 5-year crude cumulative incidence of PCa mortality for men on AA was lower than men on GnRH agonists (AA 16% [95% CI 15–18%] vs. GnRH agonists 22% [95% CI 21–24%]). The 5-year cumulative mortality incidence of other causes than PCa was also lower for men on AA than men on GnRH agonists (AA 17% [95% CI 15–19%] and GnRH agonists 27% [95% CI 25–28%]) (Figure 3).

Using the traditional Cox proportional hazards regression analyses, we found that men who received GnRH agonists had a similar risk of death from PCa as men on AA, HR 1.08 (95% CI 0.95–1.23), but a higher risk of death from all causes, HR 1.23 (95% CI 1.13–1.34) (Table 2). Stratification by PCa risk category revealed similar results, with the exception of no difference in death from all causes in men with regional metastatic PCa, HR 1.09 (95% CI 0.94–1.26).

Following propensity score matching, a total of 1972–1976 men were identified in each treatment group in the 5 imputed datasets. Similar to the results of the traditional multivariable Cox analyses, men on GnRH agonists had a similar risk of death from PCa as men on AA, HR 1.09 (95% CI 0.94–1.27), but a higher risk of death from all causes, HR 1.25 (95% CI 1.14–1.37) (Table 3). Stratification by PCa risk category revealed similar results, again with the exception of men with regionally metastatic PCa for whom there was no difference in deaths from all causes. Figure 4 shows the 1-Kaplan-Meier curves for PCa-specific death and all deaths. While there was no statistically significant difference in 5-year PCa-specific mortality, the 5-year all-cause mortality was lower for men on AA (32% [95% CI 30–35%]) than for men on GnRH agonists (42% [95% CI 39–45%)].

In a sensitivity analysis, we evaluated the effect of inclusion of imputed M1 disease in our regression models. This showed that our exclusion of M1disease attenuated the difference in risk of death between AA and GnRH agonsits, which highlights the importance of having correct staging information.

Discussion

In this register-based, observational study of men with high-risk PCa with no distant metastasis, treated with primary hormonal therapy, men on AA had similar PCa mortality and lower all-cause mortality than men on GnRH agonists.

There are two ways to interpret our results. Firstly, these findings could represent the true effect of two treatments which are known to have different mechanisms of action and different side-effect profiles. Alternatively, our results could be due to the effect of bias, given the observational nature of this study design. Even though RCTs are considered the gold standard for comparisons of treatments, it has now been recognised that clinical trials may fail to show clinical effectiveness [23]. The guidelines from the European GetReal consortium ('incorporating real-life data into drug development') specifically recommend considering evidence from pragmatic trials and non-randomised studies to improve applicability of treatment effect estimates, inform disconnected or scarce networks of evidence, identify patient populations that will likely receive the drug after launch, and to improve relevant to decision/policy makers and patients [22]. In the current register-based, observational study, all men with relevant cancer characteristics were included regardless of other characteristics, with the exception of very high age (older than 90 years of age) and a previous cancer diagnosis.

A general limitation of observational studies is the lack of randomisation and possible impact of bias caused by treatment selection. Hence, to evaluate the potential risk of bias, we used the ROBINS-I tool (Supplemental Appendix 1). After carefully assessing each of the domains outlined in the ROBINS-I tool, we concluded that the overall risk of bias was moderate. Therefore, our study provides sound evidence for

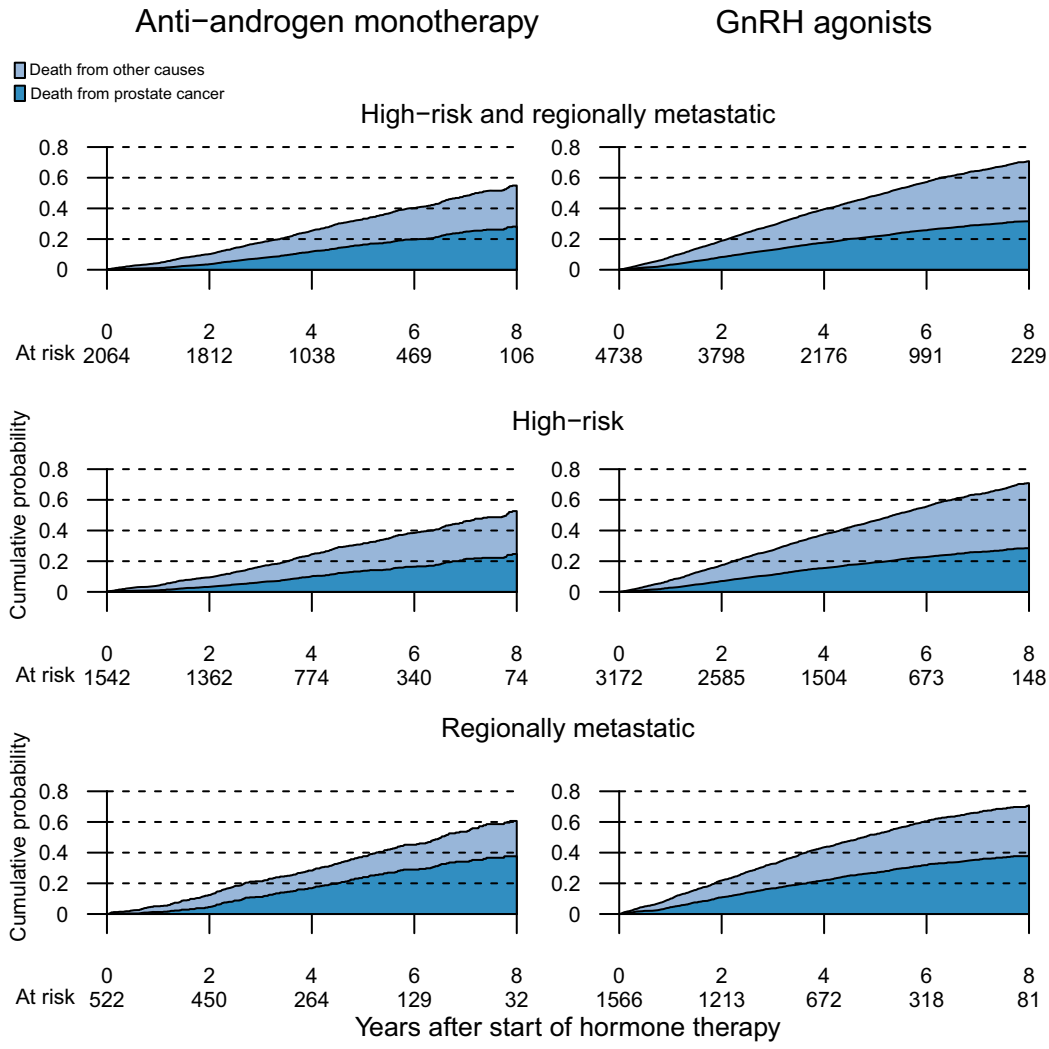

Figure 3. Cumulative probability of death from PCa or death from other causes for men on anti-androgen monotherapy (AA) and men on GnRH agonists.

a non-randomised study, but cannot be considered comparable to a well-performed RCT. Consequently, our results are deemed to be hypothesis-generating.

In the current study, men managed with AA were younger, diagnosed in more recent calendar years, had less comorbidities and had less adverse cancer characteristics compared to men treated with GnRH agonists. We adjusted for these differences in the traditional Cox regression analyses and found similar risk of PCa death in men on AA and men on GnRH agonists. However, we also observed a lower all-cause mortality among men with high-risk PCa treated with AA, while men with regional metastatic PCa had similar risk of deaths from all causes, in line with results from previous RCTs [18,19]. Unmeasured confounders are likely to account for some of this difference.

To further adjust for differences between treatment groups, we identified propensity score-matched groups of men on AA and men on GnRH agonists. A well-matched propensity score analysis is based on balanced baseline patient characteristics and excludes exposed participants who had no comparable unexposed participant and vice versa [28]. Propensity score matching does not assume linearity in the relationship between the propensity and outcome and allows for simple, transparent analyses. It provides a better balance of covariates between exposed and unexposed groups compared to other matching strategies in datasets with many covariates [29]. The propensity score-matched analyses revealed similar results as the traditional multivariable Cox regression analyses – which is not surprising given the number of detailed covariates available in this large dataset [30].

As previously mentioned, men who started on AA switched to GnRH agonists after about 4.3 years. Our results showing no difference in PCa-specific mortality and lower overall mortality in the AA group, suggest that AA can be considered as an initial alternative therapy for men with locally advanced PCa. Nevertheless, it is important to note that our study design used intention to treat rather than per protocol analysis. The former ensures comparability between groups that are obtained through randomisation (propensity score matching in this particular setting) and maintains sample size. Hence, one of the limitations of our study is potential dilution of the treatment effect estimation due to noncompliance [31].

The main limitation of our study was the non-random allocation to type of hormonal therapy, with ensuing

Table 2. Risk of death from prostate cancer or death from all causes in men on primary anti-androgen monotherapy or GnRH agonists.

	All men with high-risk and regionally metastatic prostate cancer				Men with high-risk* prostate cancer				Men with regionally metastatic** prostate cancer			
	Death from prostate cancer		Death from all causes		Death from prostate cancer		Death from all causes		Death from prostate cancer		Death from all causes	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Anti-androgen monotherapy	1.00	ref	1.00	ref	1.00	ref	1.00	ref	1.00	ref	1.00	ref
GnRH agonists												
Crude model using age as time scale	1.39	1.23–1.57	1.45	1.34–1.57	1.45	1.24–1.69	1.50	1.37–1.65	1.16	0.96–1.42	1.26	1.09–1.46
Adjustment												
T stage	1.37	1.21–1.55	1.45	1.34–1.57	1.44	1.23–1.68	1.51	1.37–1.66	1.16	0.95–1.41	1.26	1.09–1.46
Gleason Grade Group	1.21	1.07–1.37	1.37	1.27–1.48	1.25	1.07–1.47	1.44	1.30–1.58	1.06	0.87–1.29	1.19	1.03–1.37
PSA***	1.19	1.05–1.34	1.36	1.25–1.47	1.24	1.06–1.46	1.43	1.30–1.57	1.04	0.85–1.27	1.18	1.02–1.36
Proportion positive biopsy cores****	1.15	1.01–1.30	1.34	1.23–1.45	1.19	1.01–1.39	1.40	1.27–1.55	1.02	0.84–1.25	1.17	1.01–1.35
Imaging performed	1.11	0.98–1.25	1.29	1.19–1.40	1.15	0.98–1.34	1.36	1.23–1.50	0.96	0.79–1.18	1.11	0.96–1.29
Time between diagnosis and start of treatment	1.11	0.98–1.26	1.29	1.19–1.40	1.15	0.98–1.35	1.36	1.23–1.50	0.97	0.79–1.18	1.11	0.95–1.28
Mode of detection	1.10	0.97–1.25	1.28	1.18–1.39	1.13	0.96–1.33	1.34	1.21–1.48	0.96	0.78–1.18	1.10	0.95–1.28
Year of diagnosis	1.09	0.96–1.23	1.27	1.17–1.38	1.12	0.95–1.31	1.33	1.20–1.47	0.96	0.78–1.17	1.10	0.95–1.28
CCI	1.08	0.96–1.23	1.25	1.15–1.36	1.11	0.95–1.31	1.30	1.18–1.43	0.96	0.78–1.17	1.10	0.95–1.27
Marital status	1.08	0.96–1.23	1.24	1.14–1.35	1.11	0.95–1.31	1.29	1.17–1.43	0.96	0.78–1.17	1.09	0.94–1.26
Education	1.08	0.95–1.23	1.23	1.13–1.34	1.11	0.94–1.31	1.28	1.16–1.41	0.96	0.78–1.17	1.09	0.94–1.26

Hazard ratios calculated by use of Cox regression analyses.
*High-risk prostate cancer: T3 and/or PSA 20 ng/ml or higher and lower than 50 ng/ml and/or Gleason Grade Group 4–5.
**Regionally metastatic prostate cancer: T4 and/or PSA 50 ng/ml or higher and lower than 100 ng/ml or N1.
***Modelled using a linear spline with knots in PSA 3, 10, 20 and 50.
****Modelled as an interaction with T stage in men not diagnosed following TUR-P.

Table 3. Risk of death from prostate cancer or death from all causes for men on primary GnRH agonists or anti-androgen monotherapy (AA, reference in analyses) following propensity score matching.

	Including all men with a match						
		No of events		Crude		Adjusted	
	Number of men in group*	AA	GnRH	HR	95% CI	HR	95% CI
High-risk and regionally metastatic prostate cancer							
Death from prostate cancer	1975	348	371	1.09	0.94–1.26	1.05	0.90–1.23
Death from all causes	1975	702	858	1.25	1.13–1.38	1.23	1.11–1.36
High-risk prostate cancer**							
Death from prostate cancer	1436	209	239	1.15	0.91–1.45	1.12	0.88–1.42
Death from all causes	1436	473	619	1.33	1.18–1.50	1.29	1.14–1.46
Regionally metastatic prostate cancer***							
Death from prostate cancer	506	132	123	0.96	0.72–1.28	0.93	0.69–1.43
Death from all causes	506	215	237	1.11	0.89–1.37	1.12	0.89–1.40

Hazard ratios calculate by use of Cox regression analyses. The median time from diagnosis to start of treatment was 16 days longer for men on AA compared to men on GnRH agonists.
*Number of men in the first of the imputed dataset.
**High-risk prostate cancer: T3 and/or PSA 20 ng/ml or higher and lower than 50 ng/ml and/or Gleason Grade Group 4–5.
***Regionally metastatic prostate cancer: T4 and/or PSA 50 ng/ml or higher and lower than 100 ng/ml or N1.

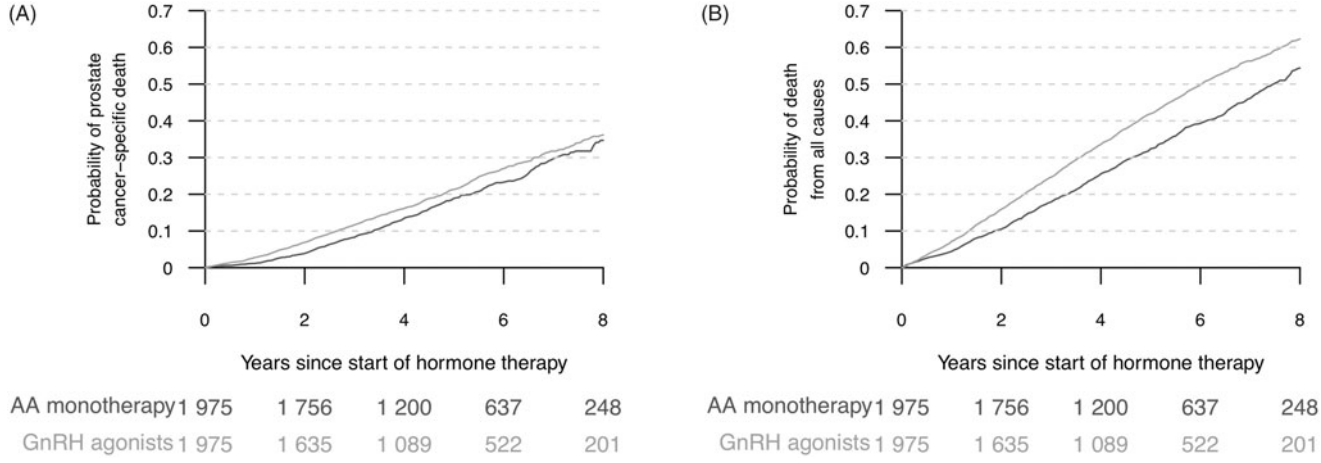

Figure 4. Probability of PCa death and death from all causes following propensity score matched for men on anti-androgen monotherapy (AA) and GnRH agonists, assessed with 1-Kaplan-Meier estimates.

channelling bias of younger and healthier men with less advanced cancer to receive AA. However, we used a robust study design with application of propensity score matching with fairly well-balanced baseline characteristics in the two treatment arms. Yet this method is based on measured variables, thus residual confounding is likely to be present as in most observational studies. Strengths of our study include the nationwide, population-based cohort of men with comprehensive data from a clinical cancer register with documented high data quality as well as several other high-quality health care registers [32,33], a setting that thus provides strong real-world data.

Conclusion

Using a hypothetical trial in a real-world setting, our results indicate that in men with high-risk PCa with no distant metastasis, PCa-specific mortality is similar for those treated with AA and those treated with GnRH agonists. However, all-cause mortality was lower for men taking AA compared with men on GnRH agonists. Starting on AA instead of GnRH agonists may result in less exposure to GnRH agonists and hence potentially less risk of adverse events.

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Disclosure statement

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References

[1] Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017;71:630–642.

[2] Guy D, Ghanem G, Loblaw A, et al. Diagnosis, referral, and primary treatment decisions in newly diagnosed prostate cancer patients in a multidisciplinary diagnostic assessment program. Can Urol Assoc J. 2016;10:120–125.

[3] Thomsen FB, Mikkelsen MK, Hansen RB, et al. Clinical characteristics and primary management of patients diagnosed with prostate cancer between 2007 and 2013: status from a Danish primary referral center. Acta Oncol. 2016;55:1456–1460.

[4] Lycken M, Garmo H, Adolfsson J, et al. Patterns of androgen deprivation therapies among men diagnosed with localised prostate cancer: a population-based study. Eur J Cancer. 2014;50:1789–1798.

[5] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017;71:618–629.

[6] Albertsen PC, Klotz L, Tombal B, et al. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol. 2014;65:565–573.

[7] Reid P, Kantoff P, Oh W. Antiandrogens in prostate cancer. Invest New Drugs. 1999;17:271–284.

[8] Crawford ED, Shore ND, Moul JW, et al. Long-term tolerability and efficacy of degarelix: 5-year results from a phase III extension trial with a 1-arm crossover from leuprolide to degarelix. Urology. 2014;83:1122–1128.

[9] Iversen P, McLeod DG, See WA, et al. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. BJU Int. 2010;105:1074–1081.

[10] Nguyen PL, Alibhai SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol. 2015;67:825–836.

[11] Thorstenson A, Bratt O, Akre O, et al. Incidence of fractures causing hospitalisation in prostate cancer patients: results from the population-based PCBaSe Sweden. Eur J Cancer. 2012;48:1672–1681.

[12] Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. Jco. 2006;24:4448–4456.

[13] Van Hemelrijck M, Garmo H, Holmberg L, et al. Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the Population-Based PCBaSe Sweden. J Clin Oncol. 2010;28:3448–3456.

[14] Nead KT, Gaskin G, Chester C, et al. Association between androgen deprivation therapy and risk of dementia. JAMA Oncol. 2017;3:49–55.

[15] Dockery F, Bulpitt CJ, Agarwal S, et al. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clin Sci. 2003;104:195–201.

[16] Malkin CJ, Pugh PJ, Jones RD, et al. Testosterone as a protective factor against atherosclerosis–immunomodulation and influence upon plaque development and stability. J Endocrinol. 2003;178:373–380.

[17] Kunath F, Grobe HR, Rucker G, et al. Non-steroidal antiandrogen monotherapy compared with luteinising hormone-releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer. Cochrane Database Syst Rev. 2014 Jun 30;(6): CD009266.

[18] Boccardo F, Rubagotti A, Barichello M, et al. Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer patients: results of an Italian Prostate Cancer Project study. J Clin Oncol. 1999;17:2027–2038.

[19] Iversen P, Tyrrell CJ, Kaisary AV, et al. Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup. J Urol. 2000;164:1579–1582.

[20] EM Agency. Bicalutamide 150 mg; 2007 [updated 2007 May 24; cited 2018 Feb 01]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Bicalutamide_150_mg/human_referral_000116.jsp

[21] Faria R, Alava MH, Manca A, Wailoo AJ. National Institute for Health and Care: the use of observational data to inform estimates of treatment effectiveness in technology appraisal: methods for comparative individual patient data; 2015. Available from:

http://nicedsu.org.uk/technical-support-documents/observational-data-tsd/

[22] Egger M, Moons KG, Fletcher C. GetReal: from efficacy in clinical trials to relative effectiveness in the real world. Res Synth Methods. 2016;7:278–281.

[23] Unger JM, Barlow WE, Martin DP, et al. Comparison of survival outcomes among cancer patients treated in and out of clinical trials. J Natl Cancer Inst. 2014;106:dju002.

[24] Van Hemelrijck M, Garmo H, Wigertz A, et al. Cohort Profile Update: The National Prostate Cancer Register of Sweden and Prostate Cancer data Base – a refined prostate cancer trajectory. Int J Epidemiol. 2016;45:73–82.

[25] Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

[26] Grundmark B, Garmo H, Zethelius B, et al. Anti-androgen prescribing patterns, patient treatment adherence and influencing factors; results from the nationwide PCBaSe Sweden. Eur J Clin Pharmacol. 2012;68:1619–1630.

[27] Van Buuren S. Flexible imputation of missing data. New York: CRC press; 2012.

[28] Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clin Pharmacol Toxicol. 2006;98:253–259.

[29] Gu XS, Rosenbaum PR. Comparison of multivariate matching methods: structures, distances, and algorithms. J Comput Graph Stat. 1993;2:405–420.

[30] Vickers AJ, Sjoberg DD, European U. Guidelines for reporting of statistics in European Urology. Eur Urol. 2015;67:181–187.

[31] Ranganathan P, Pramesh CS, Aggarwal R. Common pitfalls in statistical analysis: intention-to-treat versus per-protocol analysis. Perspect Clin Res. 2016;7:144–146.

[32] Tomic K, Berglund A, Robinson D, et al. Capture rate and representativity of The National Prostate Cancer Register of Sweden. Acta Oncol. 2015;54:158–163.

[33] Tomic K, Sandin F, Wigertz A, et al. Evaluation of data quality in the National Prostate Cancer Register of Sweden. Eur J Cancer. 2015;51:101–111.